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(19) (CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Heterocyclic Hydroxylamines

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(57) 14 Claims

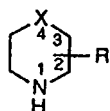
Notice: The specification contained herein as filed

**Canada**

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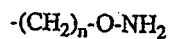
4-18498/AHeterocyclic hydroxylaminesAbstract

Compounds of formula



(I),

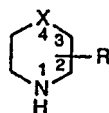
wherein X is methylene, imino, oxygen or sulfur and R is a radical



wherein n is 0, 1 or 2, with the proviso that n is other than 0 when R is bonded at the 2-position, and salts thereof, have a pronounced specific inhibitory action on the enzyme ornithine decarboxylase. The compounds of formula I are prepared by processes that are known per se.

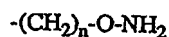
What is claimed is:

1. A compound of formula



(I)

wherein X is methylene, imino, oxygen or sulfur and R is a radical



wherein n is 0, 1 or 2, with the proviso that n is other than 0 when R is bonded at the 2-position, or a salt thereof.

2. A compound of formula I according to claim 1 wherein X is methylene, imino or oxygen, R is bonded at the 2- or 3-position and n is 1 or 2, or a salt thereof.
3. A compound of formula I according to claim 1 wherein X is methylene or oxygen, R is bonded at the 2- or 3-position and n is 1 or 2, or a salt thereof.
4. A compound of formula I according to claim 1 wherein X is methylene or oxygen, R is bonded at the 3-position and n is 1, or a salt thereof.
5. A compound of formula I according to claim 1 wherein X is methylene, R is bonded at the 4-position and n is 0 or 1, or a salt thereof.
6. A pharmaceutically acceptable salt of a compound of formula I according to any one of claims 1 to 5.
7. The compound of formula I according to claim 1 wherein X is methylene, n in the

radical R is O, and R is at the 4-position of the ring, having the name 4-aminooxy-piperidine, or a pharmaceutically acceptable salt thereof.

8. The compound of formula I according to claim 1 wherein X is oxygen, n in the radical R is 1, and R is at the 3-position of the ring, having the name 2-aminooxymethyl-morpholine, or a pharmaceutically acceptable salt thereof.

9. The compound of formula I according to claim 1 wherein X is methylene, n in the radical R is 1, and R is at the 3-position of the ring, which is numbered according to formula I, having the name 3-aminooxymethylpiperidine, or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising a compound of formula I according to any one of claims 1 to 5 and 7 to 9, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

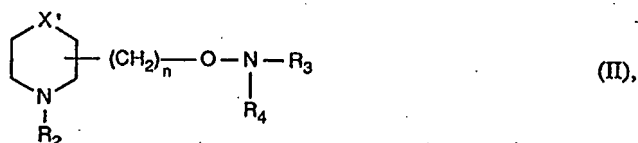
11. The use of a compound of formula I according to any one of claims 1 to 5 and 7 to 9, or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition.

12. The use of a compound of formula I according to any one of claims 1 to 5 and 7 to 9, or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment of disorders that are responsive to inhibition of the enzyme ornithine decarboxylase.

13. A compound of formula I according to any one of claims 1 to 5 and 7 to 9, or a pharmaceutically acceptable salt thereof, as an inhibitor of ornithine decarboxylase.

14. A process for the preparation of a compound of formula I according to claim 1, which comprises

(a) removing the amino-protecting group(s) from a compound of formula I wherein at least one amino group is protected, that is a compound of formula



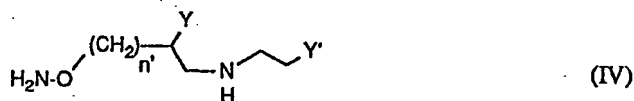
or a salt thereof, wherein  $X'$  is methylene, oxygen, sulfur or  $N-R_1$ ,  $n$  is 0, 1 or 2, with the proviso that  $n$  is other than 0 when the substituent  $-(CH_2)_n-O-NR_3R_4$  is bonded at the 2-position, and each of  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  independently of the others is an amino-protecting group or hydrogen, with the proviso that at least one of the groups  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  is an amino-protecting group, or wherein each of  $R_1$  and  $R_2$  independently of the other is an amino-protecting group or hydrogen and  $R_3$  together with  $R_4$  forms a divalent amino-protecting group, or

(b) for the preparation of a compound of formula I, or of a salt thereof, wherein  $X$  is imino or methylene, reducing a compound of formula



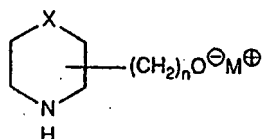
or a salt thereof, wherein  $Z$  is nitrogen or the methine group  $CH$  and  $R$  is as defined under formula I, or

(c) for the preparation of a compound of formula I, or of a salt thereof, wherein  $X$  is imino, oxygen or sulfur,  $R$  is bonded at the 2- or 3-position and  $n$  is 1 or 2, cyclising a compound of formula



wherein  $n'$  is 1 or 2 and one of the radicals  $Y$  and  $Y'$  is hydroxy, amino or sulphydryl and the other is a nucleofugal leaving group, or a salt thereof, or

(d) reacting a compound of formula



(V),

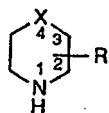
or a salt thereof, wherein  $X$  and  $n$  are as defined under formula I, with the proviso that  $n$  is other than 0 when the substituent  $-(CH_2)_nO^-M^+$  is bonded at the 2-position, and  $M^+$  is a metal cation, with a compound of the formula  $H_2N-A'$ , or with a salt thereof, wherein  $A'$  is a nucleofugal leaving group, and

if desired, converting an obtainable compound of formula I into a different compound of formula I, separating an obtainable mixture of enantiomers into the enantiomers, and/or converting an obtainable free compound of formula I into a salt or converting an obtainable salt into the free compound of formula I or into a different salt.

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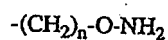
Heterocyclic hydroxylamines

The invention relates to compounds of formula:



(I)

wherein X is methylene, imino, oxygen or sulfur and R is a radical



wherein n is 0, 1 or 2, with the proviso that n is other than 0 when R is bonded at the 2-position, and their salts, to processes for the preparation of those compounds, to pharmaceutical compositions that comprise those compounds, and to the use of those compounds for the therapeutic treatment of the human or animal body and for the preparation of pharmaceutical compositions.

Within the scope of the present general description, the ring atoms are numbered starting from the nitrogen atom, that atom being numbered 1 and X being numbered 4, while numbering in the Examples is in accordance with IUPAC nomenclature.

Salts of compounds according to the invention are especially pharmaceutically acceptable acid addition salts, for example with inorganic acids, such as hydrochloric acid, sulfuric acid or phosphoric acid, or with suitable organic carboxylic or sulfonic acids, for example acetic acid, octanoic acid, succinic acid, adipic acid, fumaric acid, maleic acid, hydroxymaleic acid, propionic acid, lactic acid, malic acid, citric acid, salicylic acid, p-aminosalicylic acid, ascorbic acid, oxalic acid, benzenesulfonic acid, 1,5-naphthalenedisulfonic acid, methanesulfonic acid or 1,2-ethanedisulfonic acid, or N-cyclohexylsulfamic acid, or, for example, with amino acids, such as glutamic acid or aspartic acid. Mono- to tri-salts can be formed, depending on the number of basic groups present.

For isolation or purification purposes it is also possible to use pharmaceutically unsuitable salts, for example picrates or perchlorates. Only the pharmaceutically acceptable salts are used therapeutically, and those are therefore preferred.

The compounds of the present invention that have an asymmetric carbon atom may be in the form of pure enantiomers or in the form of mixtures of enantiomers (racemates).

The compounds according to the invention have valuable, especially pharmacologically applicable, properties. In particular, they have a pronounced, specific inhibitory action on the enzyme ornithine decarboxylase (ODC). ODC, as a key enzyme, plays an important role in polyamine biosynthesis, which takes place in virtually all mammal cells, including human cells. ODC regulates the concentration of polyamines in the cell. Inhibition of the enzyme ODC results in a reduction in the polyamine concentration. Since a reduction in the polyamine concentration brings about inhibition of cell growth, it is possible by administering ODC-inhibiting substances to inhibit the growth of both eukaryotic and prokaryotic cells, especially of cells that are growing rapidly and uncontrollably, and even to kill cells or inhibit the onset of cell differentiation.

Inhibition of the enzyme ODC can be demonstrated, for example, by the method of J.E. Seely and A.E. Pegg, Ornithine Decarboxylase (mouse kidney), pages 158-161, in H. Tabor and C. White-Tabor (ed.): Methods in Enzymology, Vol. 94: Polyamines, Academic Press, New York 1983. When ODC from rat liver is used for this assay (isolation: Hayashi, S.-I. and Kameji, T., same volume, p. 154 - 158),  $IC_{50}$ -values in the micromolar range, for example between 0,2 and 2  $\mu M$ , are obtained.  $IC_{50}$  is the concentration of the inhibitor where ODC activity is 50 % of the control without inhibitor.

As ODC-inhibitors, the compounds of formula I have anti-proliferative properties, which can be demonstrated, for example, by means of their inhibitory action on the growth of human T24 bladder carcinoma cells. That action is demonstrated by incubating the cells in Eagle's minimal essential medium, to which 5 % (v/v) foetal calf serum is added, in a humidified incubator at 37°C and with 5 % by volume  $CO_2$  in the air. 96-well microtitre plates are inoculated with the carcinoma cells (1000-1500) and incubated overnight under the said conditions. The test compound is added in a series of dilutions on day 1. The plates are incubated under the said conditions for 5 days. During that period, control cultures undergo at least 4 cell divisions. After incubation, the cells are fixed with 3.3 %



(weight/volume) aqueous glutaraldehyde solution, washed with water and stained with 0.05 % (w/v) aqueous methylene blue solution. After washing, the dye is eluted with 3 % (w/v) aqueous hydrochloric acid. The optical density (OD) per well, which is directly proportional to the number of cells, is then measured by means of a photometer (Titertek multiskan) at 665 nm. The IC<sub>50</sub> values are calculated by means of a computer system using the formula

$$\frac{OD_{665}(\text{test}) - OD_{665}(\text{start})}{OD_{665}(\text{control}) - OD_{665}(\text{start})} \times 100$$

The IC<sub>50</sub> values are defined as the concentration of active ingredient at which the number of cells per well at the end of the incubation period is only 50 % of the number of cells in the control cultures.

The compounds of formula I are suitable, for example, for treating pathological conditions that are responsive to inhibition of ornithine decarboxylase, for example benign and malignant tumours. They can bring about the regression of tumours and also prevent the spread of tumour cells and the growth of micrometastases. Moreover, they can be used, for example, for treating protozoal infections, such as, for example, trypanosomiasis, malaria, or inflammation of the lungs caused by *Pneumocystis carinii*.

The compounds of formula I can be used as selective ODC-inhibitors either on their own or in combination with other pharmacologically active substances. Combination with, for example, (a) inhibitors of other enzymes of polyamine biosynthesis, for example S-adenosylmethionine decarboxylase inhibitors, (b) inhibitors of protein kinase C, (c) inhibitors of tyrosine protein kinase, (d) cytokines, (e) negative growth regulators, (f) aromatase inhibitors, (g) anti-oestrogens or (h) conventional cytostatic active ingredients, is possible.

The invention relates preferably to compounds of formula I wherein X is methylene, imino or oxygen, R is bonded at the 2- or 3-position and n is 1 or 2, and to compounds of formula I wherein X is methylene, R is bonded at the 4-position and n is 0 or 1, and salts thereof.

Special mention is to be made of compounds of formula I wherein X is methylene or

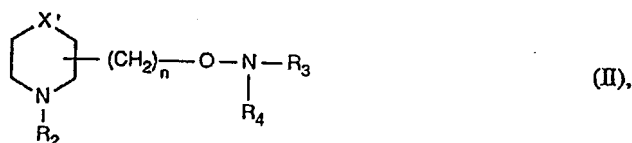
oxygen, R is bonded at the 2- or 3-position and n is 1 or 2, and of compounds of formula I wherein X is methylene, R is bonded at the 4-position and n is 0 or 1, and salts thereof.

Special preference is given to compounds of formula I wherein X is methylene or oxygen, R is bonded at the 3-position and n is 1, or wherein X is methylene, R is bonded at the 4-position and n is 0, and salts thereof.

The invention relates especially to the specific compounds described in the Examples, and to pharmaceutically acceptable salts thereof.

The novel compounds of formula I can be prepared in a manner known per se, for example by

(a) removing the amino-protecting group(s) from a compound of formula I wherein at least one amino group is protected, for example a compound of formula



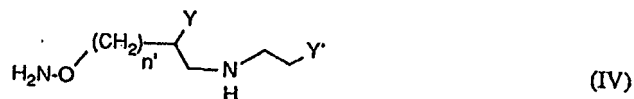
or a salt thereof, wherein X' is methylene, oxygen, sulfur or N-R<sub>1</sub>, n is 0, 1 or 2, with the proviso that n is other than 0 when the substituent -(CH<sub>2</sub>)<sub>n</sub>-O-NR<sub>3</sub>R<sub>4</sub> is bonded at the 2-position, and each of R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> independently of the others is an amino-protecting group or hydrogen, with the proviso that at least one of the groups R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> is an amino-protecting group, or wherein each of R<sub>1</sub> and R<sub>2</sub> independently of the other is an amino-protecting group or hydrogen and R<sub>3</sub> together with R<sub>4</sub> forms a divalent amino-protecting group, or

(b) for the preparation of compounds of formula I, or of a salt thereof, wherein X is imino or methylene, reducing a compound of formula



or a salt thereof, wherein Z is nitrogen or the methine group CH and R is as defined under formula I, or

(c) for the preparation of compounds of formula I, or of a salt thereof, wherein X is imino, oxygen or sulfur, R is bonded at the 2- or 3-position and n is 1 or 2, cyclising a compound of formula



wherein  $n'$  is 1 or 2 and one of the radicals Y and Y' is hydroxy, amino or sulfhydryl and the other is a nucleofugal leaving group, or a salt thereof, or

(d) reacting a compound of formula



or a salt thereof, wherein X and n are as defined under formula I, with the proviso that n is other than 0 when the substituent  $-(\text{CH}_2)_n\text{O}^\ominus\text{M}^\oplus$  is bonded at the 2-position, and  $\text{M}^\oplus$  is a metal cation, with a compound of the formula  $\text{H}_2\text{N}-\text{A}'$ , or with a salt thereof, wherein A' is a nucleofugal leaving group, and

if desired, converting an obtainable compound of formula I into a different compound of formula I, separating an obtainable mixture of enantiomers into the enantiomers, and/or converting an obtainable free compound of formula I into a salt or converting an obtainable salt into the free compound of formula I or into a different salt.

Salts of starting materials that have at least one basic centre, for example compounds of formula III, are corresponding acid addition salts.

Within the scope of the present Application, the prefix "lower" used hereinafter denotes a

radical having from 1 to 7 and especially from 1 to 4 carbon atoms. Lower alkyl is, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl or heptyl, it being possible for an alkyl radical having from 3 to 7 carbon atoms to be straight-chained or branched.

Process (a): Preferred monovalent amino-protecting groups  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  are acyl groups, for example lower alkanoyl, such as formyl, acetyl or propionyl, halo-lower alkanoyl, such as 2-haloacetyl, especially 2-chloro-, 2-bromo-, 2-iodo-, 2,2,2-trifluoro- or 2,2,2-trichloro-acetyl, benzoyl that is unsubstituted or substituted, for example by halogen, lower alkoxy, lower alkoxycarbonyl or by nitro, for example benzoyl, 4-chlorobenzoyl, 4-methoxybenzoyl, 2-methoxycarbonylbenzoyl or 4-nitrobenzoyl, arylmethoxycarbonyl having one or two aryl radicals, which aryl radicals are especially phenyl that is unsubstituted or mono- or poly-substituted, for example by lower alkyl, especially tert-lower alkyl, such as tert-butyl, lower alkoxy, such as methoxy, hydroxy, halogen, for example chlorine, and/or by nitro, such as unsubstituted or substituted benzyloxycarbonyl, for example 4-nitrobenzyloxycarbonyl, or substituted diphenylmethoxycarbonyl, for example di(4-methoxyphenyl)methoxycarbonyl, 2-halo-lower alkoxycarbonyl, for example 2,2,2-trichloroethoxycarbonyl, 2-bromomethoxycarbonyl or 2-iodoethoxycarbonyl, or a lower alkoxycarbonyl radical that is branched at the 1-position of the lower alkyl radical or suitably substituted at the 1- or 2-position, especially tert-lower alkoxycarbonyl, for example tert-butoxycarbonyl, or arylmethyl groups, such as mono-, di- or, especially, tri-aryl-methyl, the aryl radicals being especially unsubstituted or substituted phenyl radicals, for example benzyl, diphenylmethyl or triphenylmethyl (trityl).

Especially preferred monovalent amino-protecting groups  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  are acyl radicals of carbonic acid semi-esters, especially tert-butoxycarbonyl, unsubstituted benzyloxycarbonyl or benzyloxycarbonyl that is substituted, for example, as indicated above, for example 4-nitrobenzyloxycarbonyl, diphenylmethoxycarbonyl, or 2-halo-lower alkoxy-carbonyl, such as 2,2,2-trichloroethoxycarbonyl, and also trityl or formyl.

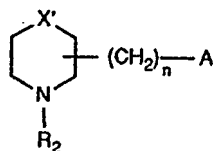
Preferred divalent amino-protecting groups formed from the radicals  $R_3$  and  $R_4$  are mono- or di-substituted methylenide groups, such as 1-lower alkoxy (for example methoxy or ethoxy)-lower alkylidene (for example ethylidene or 1-n-butylidene), for example  $=C(CH_3)(OC_2H_5)$ , and also, for example,  $=C(CH_3)_2$  or  $=CH$ -phenyl, and especially bis-acyl radicals, for example the phthalyl radical which, together with the nitrogen atom to be protected, forms a 1H-isindole-1,3(2H)-dione (phthalimido group).

Amino-protecting groups, their introduction and removal are known per se and are described, for example, in J.F.W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London, New York, 1973, and T.W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York, 1984.

The removal of the amino-protecting group(s) is effected, optionally in stages or simultaneously, depending on the nature of the protecting group(s), in a manner known per se, for example by means of reduction or solvolysis, especially hydrolysis, preferably in an acidic medium, alcoholysis, acidolysis or hydrazinolysis. The tert-butoxycarbonyl group or the trityl radical can be freed, for example, by treatment with an acid, such as a mineral acid, for example hydrochloric acid, in the absence or presence of solvents, especially methanol or tetrahydrofuran, or an organic acid, for example formic, acetic or trifluoroacetic acid, in the absence or presence of water or of an organic solvent, for example methylene chloride. The unsubstituted or substituted benzyloxycarbonyl group is removed, for example, reductively by hydrogenolysis, i.e. by treatment with hydrogen in the presence of a suitable catalyst, for example palladium, or by means of sodium in liquid ammonia, or by acidolysis, especially by means of hydrogen bromide/glacial acetic acid. 2-halo-lower alkoxy carbonyl can be removed, for example, by treatment with a suitable reducing agent, such as zinc, in the presence of an organic solvent, such as methanol or aqueous acetic acid. Removal of the phthalyl group can be effected, for example, by means of hydrazine hydrate or by means of an acid, for example a mineral acid, such as hydrochloric acid, in the absence or presence of organic solvents, for example methanol.

The starting materials of formula II are known or are prepared according to processes known per se [cf., for example, Houben-Weyl, Methoden der Organischen Chemie, Vol. X/1 (1971) and Vol. E 16a (1990)].

The starting materials of formula II are prepared, for example, by reacting a compound of formula



(VI),

wherein X', R<sub>2</sub> and n are as defined under formula II and A is hydroxy or a nucleofugal

leaving group, with N-protected or unprotected hydroxylamine.

When A in a compound of formula VI is hydroxy, then, for example, an intermolecular dehydration reaction may be carried out. Especially suitable for that purpose is a variant of the Mitsunobu reaction [Synthesis (1976), 682], in which the compound of formula VI is reacted with an N-protected hydroxylamine derivative, for example N-hydroxyphthalimide, N-hydroxy-5-norbornene-2,3-dicarboxylic acid imide or acetohydroxamic acid ethyl ester, and, for example, triphenylphosphine and N,N'-azodicarboxylic acid diethyl ester.

The nucleofugal leaving group A in the compounds of formula VI is, for example, sulfonyloxy that carries aliphatic - or aromatic - substituents, for example methane-sulfonyloxy or p-toluenesulfonyloxy (tosyloxy), but may also be, for example, halogen, especially chlorine, bromine or iodine. Corresponding compounds of formula VI are reacted in a simple nucleophilic substitution with N-protected hydroxylamine derivatives, for example those mentioned above.

Compounds of formula II can also be prepared by carrying out one of processes (b), (c) or (d) with protected amino group(s). Furthermore, compounds of formula II can also be prepared from compounds of formula I - for example for purification purposes.

Process (b): Compounds of formula III are converted into the corresponding hexahydro derivatives of formula I by reduction, for example with an alkaline earth metal or an alkaline metal, for example sodium, in a lower alkanol, such as ethanol, by electrolytic reduction, or by reduction with complex metal hydrides, for example sodium or lithium aluminium hydride, or sodium or lithium borohydride, or, especially, with hydrogen in the presence of a transition metal catalyst [cf. M. Hudlicky, Reductions in Organic Chemistry, Ellis Horwood Limited (1984)]. The catalytic hydrogenation is carried out, for example, with palladium, platinum oxide or rhodium, optionally with the addition of carbon, preferably in an acidic medium, for example in glacial acetic acid, or with ruthenium dioxide, Raney nickel or copper chromite. Compounds of formula III are known or are prepared by processes known per se.

Process (c): A nucleofugal leaving group Y or Y' is, for example, hydroxy or a reactive esterified hydroxy group, such as hydroxy esterified by a strong inorganic acid or organic sulfonic acid, for example halogen, such as chlorine, bromine or iodine, or sulfonyloxy,

such as hydroxysulfonyloxy, halosulfonyloxy, for example fluorosulfonyloxy, lower alkanesulfonyloxy that is unsubstituted or substituted, for example by halogen, for example methane- or trifluoromethane-sulfonyloxy, cycloalkanesulfonyloxy, for example cyclohexanesulfonyloxy, or benzenesulfonyloxy that is unsubstituted or substituted, for example by lower alkyl or by halogen, for example p-bromobenzene- or p-toluene-sulfonyloxy.

Preferably, Y is hydroxy, amino or sulfhydryl and Y' is a nucleofugal leaving group, for example one of those mentioned above.

Compounds of formula IV wherein one of the radicals Y and Y' is hydroxy, amino or sulfhydryl and the other is a nucleofugal leaving group, for example one of those mentioned above, can be converted into compounds of formula I, for example in the presence of a condensing agent, such as a suitable base. Examples of suitable bases are inorganic bases, such as alkali metal hydroxides, for example sodium hydroxide solution, or, especially, organic bases, for example lower alkylamines, such as di- or tri-ethylamine, basic heterocycles, for example of the pyridine type, for example pyridine, or alkali metal alkanolates, for example potassium tert-butanolate.

In an especially preferred form of process, for example, a compound of formula IV wherein Y is hydroxy, amino or sulfhydryl and Y' is hydroxy is reacted with sulfonyl chloride that carries aliphatic - or aromatic - substituents, for example methanesulfonyl chloride or tosyl chloride (p-toluenesulfonyl chloride), in the presence of an inorganic or organic base, for example pyridine, a further reaction taking place in situ under the reaction conditions to form the desired end product of formula I, or a salt thereof.

Especially in the case of the last-mentioned reaction, it may be necessary before carrying out the reaction to protect the amino groups in the compounds of formula IV by amino-protecting groups, for example those mentioned in process (a). After the reaction, the amino-protecting groups are removed again in a manner known per se.

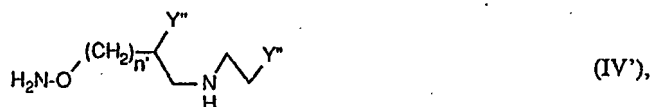
Compounds of formula IV wherein Y and Y' are both hydroxy can be cyclised to form compounds of formula I wherein X is oxygen, for example in the presence of strong acids, for example sulfuric acid, or hydrofluoric acid, in the absence or presence of sulfur tetrafluoride, or in the presence of acidic ion exchangers.

Furthermore, compounds of formula IV wherein one of the radicals Y and Y' is hydroxy or sulfhydryl and the other is hydroxy can be cyclised to form morpholine or thio-morpholine derivatives of formula I, for example by reaction with fluorinating agents that are suitable, for example, for converting hydroxy into fluorine, for example hydrogen fluoride, sulfur tetrafluoride, especially a mixture of hydrogen fluoride and sulfur tetrafluoride, and also substituted aminosulfur trifluorides, such as diethylaminosulfur trifluoride (DAST) or piperidinosulfur trifluoride.

The starting materials of formula IV are known or are prepared by processes that are known per se.

The starting materials of formula IV wherein Y and/or Y' are sulfonyloxy that carries aliphatic - or aromatic - substituents are preferably prepared in a manner known per se from compounds of formula IV wherein Y and/or Y' are hydroxy, for example by reaction with lower alkane chlorides or arenesulfonyl chlorides.

Furthermore, starting materials of formula IV wherein Y or Y' is amino or sulfhydryl can be prepared in situ, for example by reacting a compound of formula

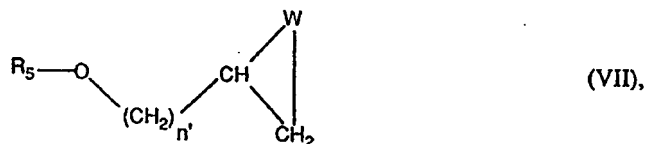


wherein n' is as defined under formula IV and each Y'' is a nucleofugal leaving group, for example one of those mentioned above, with ammonia or sodium sulfide, the compound of formula IV formed initially reacting further immediately under the given reaction conditions.

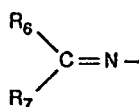
If appropriate, the amino groups in the compounds of formula IV' may be protected by amino-protecting groups, for example those mentioned in process (a), before the reaction is carried out and then freed at any stage of the process in a manner known per se.

The starting materials of formula IV wherein Y is hydroxy or sulfhydryl and Y' is hydroxy are prepared, for example, by reacting with ethanolamine a compound of formula





wherein  $n'$  is as defined under formula IV, W is oxygen or sulfur and  $\text{R}_5$  is a protected amino group, for example one of those mentioned in process (a), or is a radical



wherein, for example,  $\text{R}_6$  is lower alkyl, lower alkoxy-lower alkyl, for example methoxymethyl or ethoxymethyl, or phenyl, and  $\text{R}_7$  is hydrogen, lower alkyl or lower alkoxy, for example n-propoxy, isopropoxy, n-butoxy or tert-butoxy, preferably methoxy and especially ethoxy, or  $\text{R}_6$  and  $\text{R}_7$  together are  $\text{C}_4$ - $\text{C}_6$ alkylene or benzo- $\text{C}_4$ - $\text{C}_6$ alkylene, and then freeing the protected amino group, for example in the manner described above, or

hydrolysing the group  $\begin{array}{c} \text{R}_6 \\ \diagdown \\ \text{C}=\text{N}- \\ \diagup \\ \text{R}_7 \end{array}$ .

A radical  $\text{R}_6\text{R}_7\text{C}=\text{N}-$  wherein  $\text{R}_6$  and  $\text{R}_7$  together are  $\text{C}_4$ - $\text{C}_6$ alkylene is to be understood as being cycloalkylideneamino having from 5 to 7 ring carbon atoms, for example cyclopentylideneamino or cyclohexylideneamino.

A radical  $\text{R}_6\text{R}_7\text{C}=\text{N}-$  wherein  $\text{R}_6$  and  $\text{R}_7$  together are benzo- $\text{C}_4$ - $\text{C}_6$ alkylene is to be understood as being, for example, cyclopentylideneamino or cyclohexylideneamino each of which carries a fused benzo ring.

The reaction of compounds of formula VII with ethanolamine is carried out without a solvent or in the presence of a solvent, for example a lower alkanol or ether, such as isopropanol or tetrahydrofuran, and optionally under elevated pressure, and takes place selectively at the terminal carbon atom of the oxiranyl or thiiranyl radical.

The starting materials of formula VII wherein W is oxygen are obtained, for example, by

reacting a hydroxylamine or oxime of the formula  $R_5\text{-OH}$  with, for example, epichlorohydrin, epibromohydrin or 3-tosyloxy-1,2-epoxypropane. Starting materials of formula VII wherein W is sulfur are formed, for example, in the reaction of a hydroxylamine or oxime of the formula  $R_5\text{-OH}$  with thioepichlorohydrin. These reactions are preferably carried out in the presence of a base, for example sodium hydroxide, and without a solvent or in the presence of a solvent, for example acetone or acetonitrile.

Process (d): A metal cation  $M^\oplus$  is, for example, the cation of an alkali metal, for example potassium, sodium or lithium, or a cation  $1/2 (M_1^{2\oplus})$ , where  $M_1$  is an alkaline earth metal, such as magnesium, calcium or barium.

A nucleofugal leaving group  $A'$  is, for example, a reactive esterified hydroxy group, for example one of those mentioned under process (c).

In a preferred form of process, for example, metal salts of formula V wherein  $M^\oplus$  is a sodium cation are reacted with a halogenamine, for example chloramine, or with the sodium salt of hydroxylamine-O-sulfonic acid to form a compound of formula I.

Metal salts of formula V are formed, for example, when metals, especially alkaline earth metals or alkali metals, act on corresponding alcohols with the evolution of hydrogen, or by the reaction of alcohols with suitable bases, such as an alkali metal hydride or amide.

The invention relates especially to the compounds and processes described in the Examples.

Salts of compounds of formula I can be prepared in a manner known per se, for example by treatment with an acid, such as an inorganic acid, for example hydrochloric acid or sulfuric acid, an organic carboxylic acid, for example adipic acid, or an organic sulfonic acid, for example benzenesulfonic acid, or with a suitable anion exchange reagent which is charged, for example, with the corresponding acid. Salts can be converted into the free compounds in customary manner, for example by treatment with a suitable basic agent, such as a hydroxy base in free solution, for example an alkali metal hydroxide, or an anion exchanger charged with hydroxide, for example by chromatography or in a batch process.

The direct conversion of an acid addition salt of one of the compounds of formula I and an acid by means of a different acid into an acid addition salt of the compound of formula I

and the second, new acid is also possible. This conversion can be carried out by reaction of the starting acid addition salt a) in free solution in the presence of a suitable amount of the new acid, for example an excess, or b) on an anion exchanger charged with the anion of the new acid.

For all reactions that serve to convert acid addition salts of bases of formula I into different acid addition salts or into the free compounds, or to convert the free bases into the corresponding acids, gel-chromatographic methods may also be employed.

Depending on the procedure and the reaction conditions, the compounds according to the invention having salt-forming basic properties may be obtained in free form or in the form of salts.

The compounds, including their salts, may also be obtained in the form of their hydrates, or their crystals may include, for example, the solvent used for crystallisation.

Mixtures of enantiomers obtainable according to the invention can be separated into individual enantiomers in a manner known *per se*, for example by the formation of salts with optically pure salt-forming reagents and separation of the diastereoisomeric mixture so obtainable, for example by means of fractional crystallisation.

The above-mentioned reactions can be carried out under reaction conditions that are known *per se*, in the absence or, customarily, in the presence of solvents or diluents, preferably solvents or diluents that are inert towards and dissolve the reagents used, in the absence or presence of catalysts, condensing agents or neutralising agents, depending on the nature of the reaction and/or of the reactants at reduced, normal or elevated temperature, for example in a temperature range of from approximately  $-80^{\circ}\text{C}$  to approximately  $190^{\circ}\text{C}$ , preferably from approximately  $-20^{\circ}\text{C}$  to approximately  $150^{\circ}\text{C}$ , for example at room temperature, at from  $-20$  to  $20^{\circ}\text{C}$  or at the boiling point of the solvent used, under atmospheric pressure or in a closed vessel, optionally under pressure, and/or in an inert atmosphere, for example under a nitrogen atmosphere.

The solvents from which those solvents that are suitable for the particular reaction may be selected include, for example, water, ethers, such as aliphatic ethers, for example diethyl ether, or cyclic ethers, for example tetrahydrofuran, liquid aromatic hydrocarbons, such as benzene or toluene, alcohols, such as methanol, ethanol or 1- or 2-propanol, nitriles, such

as acetonitrile, halogenated hydrocarbons, such as methylene chloride, acid amides, such as dimethylformamide, bases, such as heterocyclic nitrogen bases, for example pyridine, or mixtures of these solvents, for example aqueous solutions, unless otherwise indicated in the description of the processes.

In the processes of the present invention there are preferably used those starting materials which result in the compounds that have been described at the beginning as being especially valuable.

The invention relates also to those forms of the process in which a compound obtainable as intermediate at any stage of the process is used as starting material and the remaining process steps are carried out or the process is discontinued at any stage, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example a salt.

The present invention relates also to pharmaceutical compositions that comprise one of the pharmacologically active compounds of formula I as active ingredient. Compositions for enteral, especially oral, and parenteral administration are especially preferred. The compositions comprise the active ingredient on its own or, preferably, together with a pharmaceutically acceptable carrier. The dose of active ingredient depends on the disease to be treated, and on the species, its age, weight and individual condition, and on the mode of administration.

The pharmaceutical compositions comprise from approximately 5 % to approximately 95 % active ingredient, dosage forms that are in single dose form preferably comprising from approximately 20 % to approximately 90 % active ingredient, and dosage forms that are not in single dose form preferably comprising from approximately 5 % to approximately 20 % active ingredient. Unit dose forms, such as dragées, tablets or capsules, comprise from approximately 0.05 g to approximately 1.0 g of active ingredient.

The pharmaceutical compositions of the present invention are prepared in a manner known per se, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes. For example, pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with one or more solid carriers, optionally granulating a resulting mixture, and processing the mixture or granules, if desired and/or appropriate, by the addition of additional excipients, to form

tablets or dragée cores.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tri-calcium phosphate or calcium hydrogen phosphate, and also binders, such as starches, for example corn, wheat, rice or potato starch, methylcellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches and also carboxymethyl starch, cross-linked polyvinylpyrrolidone, alginic acid or a salt thereof, such as sodium alginate. Additional excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol, or derivatives thereof.

Dragée cores can be provided with suitable, optionally enteric coatings, there being used inter alia concentrated sugar solutions, which may comprise gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate. Colourings or pigments may be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

Pharmaceutical compositions for oral administration are also hard gelatin capsules, and soft sealed capsules consisting of gelatin and a plasticiser, such as glycerol or sorbitol. The hard gelatin capsules may contain the active ingredient in the form of granules, for example in admixture with fillers, such as corn starch, binders and/or glidants, such as talc or magnesium stearate, and optionally stabilisers. In soft capsules the active ingredient is preferably dissolved or suspended in suitable liquid excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols, it likewise being possible to add stabilisers.

Other oral dosage forms are, for example, syrups prepared in customary manner which comprise the active ingredient, for example, in suspended form and in a concentration of approximately from 5 % to 20 %, preferably approximately 10 % or in a similar concentration that provides a suitable single dose when administered, for example, in a measure of 5 or 10 ml. Also suitable are, for example, powdered or liquid concentrates for the preparation of shakes, for example in milk. Such concentrates may also be packed in

single dose quantities.

Suitable rectally administrable pharmaceutical compositions are, for example, suppositories that consist of a combination of the active ingredient with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols.

For parenteral administration there are suitable, especially, aqueous solutions of an active ingredient in water-soluble form, for example in the form of a water-soluble salt, or aqueous injection suspensions that comprise viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, if desired, stabilisers. The active ingredient, optionally together with excipients, can also be in the form of a lyophilisate and be made into a solution prior to parenteral administration by the addition of suitable solvents.

Solutions used, for example, for parenteral administration can also be used as infusion solutions.

The invention relates also to a method of treating the pathological conditions mentioned above in warm-blooded animals, i.e. humans and animals, especially warm-blooded animals in need of such treatment. The compounds of the present invention can be administered prophylactically or therapeutically. They are preferably used in the form of pharmaceutical compositions, for example in a dose that is suitable for inhibiting ornithine decarboxylase and is effective prophylactically or therapeutically against one of the mentioned disorders, for example tumours or protozoal infections. For a body weight of approximately 70 kg, a daily dose of from approximately 0.3 g to approximately 15 g, preferably from approximately 0.5 g to approximately 5 g, of a compound of the present invention is administered. The pharmaceutical compositions are preferably compositions that are suitable for administration to a warm-blooded animal, for example a human being, for the treatment or prophylaxis of one of the above-mentioned disorders that is responsive to inhibition of ornithine decarboxylase, and comprise an amount of a compound of formula I, or of a salt thereof, that is effective in inhibiting that enzyme, optionally together with at least one carrier.

The following Examples illustrate the present invention; temperatures are given in degrees Celsius. The following abbreviations are used: ethyl acetate  $\hat{=}$  acetic acid ethyl ester;

BOC  $\hat{=}$  tert-butoxycarbonyl; ether  $\hat{=}$  diethyl ether; conc.  $\hat{=}$  concentrated;  $R_f$   $\hat{=}$  ratio of distance moved to solvent front in thin-layer chromatography; m.p.  $\hat{=}$  melting point; decomp.  $\hat{=}$  with decomposition.

Example 1: 4-Aminooxypiperidine dihydrochloride

16.1 g (0.04648 mol) of 2-(N-BOC-4-piperidyloxy)-1H-isoindole-1,3(2H)-dione are suspended, with stirring, in 100 ml of 6N hydrochloric acid. The reaction mixture is heated at 100° for 2 hours to form a clear solution with evolution of CO<sub>2</sub>, from which after a short time a crystalline precipitate (phthalic acid) forms. The reaction mixture is cooled to 0°C, filtered, the filtration product is washed with water, and the filtrate is concentrated by evaporation in vacuo. The residue is taken up in ethanol and concentrated to dryness by evaporation in vacuo. After a further addition of ethanol, concentrating by evaporation in vacuo and recrystallising the residue from methanol/ether, the title compound is obtained, m.p. 182°C (decomp.). Unless otherwise indicated, solvent ratios refer to volume (v/v).

The starting material is prepared as follows:

a) 2-(N-BOC-4-piperidyloxy)-1H-isoindole-1,3(2H)-dione  
14.07 ml (0.08415 mol) of azodicarboxylic acid diethyl ester (93 %) are added dropwise at 30-35°C, with stirring and under a nitrogen atmosphere, to a solution of 16 g (0.07947 mol) of N-BOC-4-hydroxypiperidine (see EP 0 278 621), 12.97 g (0.07947 mol) of N-hydroxyphthalimide and 20.85 g (0.07947 mol) of triphenylphosphine in 160 ml of tetrahydrofuran. The reaction mixture is stirred for a further 2 hours at room temperature and is then concentrated by evaporation in vacuo. In order to remove 1,2-hydrazine-dicarboxylic acid diethyl ester and triphenylphosphine oxide, the oily residue is dissolved in ethyl acetate, cooled to 0°C and filtered and the filtrate is concentrated by evaporation, and then the same procedure is repeated once more, but using ether. The residue obtained after evaporation of ether is purified by means of flash chromatography on silica gel having a particle size of from 0.04 to 0.063 mm, using ethyl acetate/hexane mixtures (1:2 and 2:3). Concentration of the product-containing fractions by evaporation and recrystallisation of the residue from methylene chloride/hexane yield the title compound, m.p. 119-121°C.

2-(N-BOC-4-piperidyloxy)-1H-isoindole-1,3(2H)-dione can also be obtained from

4-hydroxypiperidine as follows:

b) A solution of 10.92 g (0.05 mol) of di-tert-butyl dicarbonate in 30 ml of toluene is added dropwise to a mixture of 5.06 g (0.05 mol) of 4-hydroxypiperidine in 50 ml of toluene, and the mixture is stirred at room temperature for 4 days. To the resulting solution of N-BOC-4-hydroxypiperidine in toluene there are added, with continued stirring and under a nitrogen atmosphere, 8.16 g (0.05 mol) of N-hydroxyphthalimide and 13.11 g (0.05 mol) of triphenylphosphine. A solution of 8.85 ml (0.0529 mol) of azodicarboxylic acid diethyl ester (93 %) in 20 ml of toluene is then added dropwise at 30-35°C, and the reaction mixture is stirred for a further 15 hours at room temperature. The mixture is cooled to 5°C, the resulting hydrazinedicarboxylic acid diethyl ester is filtered off, the filtrate is concentrated by evaporation *in vacuo*, and the residue is purified by means of flash chromatography on silica gel using ethyl acetate/hexane mixtures (1:3 and 1:2). Concentration of the product-containing fractions by evaporation yields the title compound in the form of a crystalline residue, m.p. 116-118°C.

c) 4-Aminooxypiperidine dihydrochloride can also be obtained as follows:

A mixture of 1.414 g (0.005 mol) of 2-(4-piperidyloxy)-1H-isoindole-1,3(2H)-dione hydrochloride and 10 ml of 6N HCl is heated at 100° for 2 hours and then worked up analogously to Example 1, yielding the title compound, m.p. 182°C (decomp.).

The starting material is prepared as follows:

d) 2-(4-Piperidyloxy)-1H-isoindole-1,3(2H)-dione hydrochloride

Hydrogen chloride gas is introduced, with stirring and while cooling with an ice-bath, into a solution of 3.46 g (0.01 mol) of 2-(N-BOC-4-piperidyloxy)-1H-isoindole-1,3(2H)-dione in 40 ml of tetrahydrofuran. A crystalline suspension forms after only a short time and is left to stand at room temperature for 15 hours. After filtering the crystallisate and washing the filtration product with tetrahydrofuran the title compound is obtained, m.p. 242-243°C.

Example 2: 4-Aminooxypiperidine dihydrochloride

A mixture of 1.57 g (0.005 mol) of 2-Methoxycarbonyl-(N-(4-piperidyloxy)-benzoic amide hydrochloride and 10 ml of 2N hydrochloric acid is heated at 100° for 2 hours and worked up analogously to Example 1, yielding the title compound, m.p. 182°C (decomp.).



The starting material is prepared as follows:

a) 2-Methoxycarbonyl-(N-(4-piperidylloxy)-benzoic amide hydrochloride

A mixture of 5 g (0.01443 mol) of 2-(N-BOC-4-piperidylloxy)-1H-indole-1,3(2H)-dione and 100 ml of a 1.3N solution of hydrogen chloride in methanol is stirred at room temperature for 2 hours and then concentrated by evaporation *in vacuo*. On subjecting the residue to fractional recrystallisation from ethanol, 2-(4-piperidylloxy)-1H-indole-1,3(2H)-dione hydrochloride, m.p. 240-241°C, is precipitated first, and on subsequently concentrating the mother liquor, the title compound, m.p. 179-180°C (decomp.), is precipitated.

Example 3: 3-Aminooxymethylpiperidine dihydrochloride

The title compound having a water content of 1.74 %, m.p. 191°C (decomp.), is obtained analogously to Example 1 starting from 6 g (0.0166 mol) of 2-(N-BOC-3-piperidylmethoxy)-1H-indole-1,3(2H)-dione and 40 ml of 6N hydrochloric acid.

The starting material is prepared as follows:

a) 2-(N-BOC-3-piperidylmethoxy)-1H-indole-1,3(2H)-dione

Analogously to Example 1a, 6.46 g (0.03 mol) of N-BOC-3-hydroxymethylpiperidine (see EP 0 279 681), 4.90 g (0.03 mol) of N-hydroxyphthalimide, 7.87 g (0.03 mol) of triphenylphosphine and 5.3 ml (0.0317 mol) of azodicarboxylic acid diethyl ester (93 %) are reacted in 70 ml of tetrahydrofuran. Purification of the crude product by means of flash chromatography on silica gel using ethyl acetate/hexane mixtures (1:3 and 1:2) and concentration of the product-containing fractions by evaporation yield the title compound in the form of a crystalline residue, m.p. 92-94°C.

Example 4: 2-(2-Aminooxyethyl)piperidine dihydrochloride

A mixture of 6 g (0.01602 mol) of 2-(N-BOC-2-piperidylethoxy)-1H-indole-1,3(2H)-dione and 40 ml of 6N hydrochloric acid is reacted analogously to Example 1. Crystallisation twice from ethanol/ether yields the title compound, m.p. 129-132°C (decomp.).

The starting material is prepared as follows:

a) 2-(N-BOC-2-piperidylethoxy)-1H-indole-1,3(2H)-dione

Analogously to Example 1a, 6.9 g (0.03 mol) of N-BOC-2-(2-hydroxyethyl)piperidine

(see EP 0 289 842), 4.9 g (0.03 mol) of N-hydroxyphthalimide, 7.87 g (0.03 mol) of triphenylphosphine and 5.3 ml (0.0317 mol) of azodicarboxylic acid diethyl ester (93 %) are reacted in 70 ml of tetrahydrofuran. Removal of the by-products (1,2-hydrazinedicarboxylic acid diethyl ester and triphenylphosphine oxide) and concentration of the ethereal filtrates yield the title compound in the form of a crystalline residue, m.p. 108°C.

Example 5: 4-Aminooxymethylpiperidine dihydrochloride

A mixture of 0.5 g (0.00217 mol) of N-BOC-4-aminooxymethylpiperidine and 10 ml of 1.3N methanolic hydrochloric acid is stirred at room temperature for one hour and then concentrated by evaporation in vacuo. Recrystallisation of the residue from methanol/ether yields the title compound, m.p. 199-200°C (decomp.).

The starting materials are prepared as follows:

a) N-BOC-4-aminooxymethylpiperidine

A mixture of 3.5 g (0.00971 mol) of 2-(N-BOC-4-piperidylmethoxy)-1H-isoindole-1,3(2H)-dione and 20 ml of hydrazine hydrate is stirred at room temperature for 2 hours, then 75 ml of ether are added and the mixture is stirred for a further 2 hours. The organic phase is then separated off and the hydrazine hydrate phase is extracted twice with 50 ml of ether each time. The combined ethereal phases are washed with water and saturated sodium chloride solution, dried over sodium sulfate and concentrated by evaporation in vacuo, yielding the title compound in the form of a colourless oil,  $R_f$ : 0.60 [TLC ready-prepared plates, silica gel 60 F<sub>254</sub>; eluant: methylene chloride/methanol (9:1)].

b) 2-(N-BOC-4-piperidylmethoxy)-1H-isoindole-1,3(2H)-dione

Analogously to Example 1a, but with a reaction time of 17 hours, the title compound, m.p. 109-110°C, is obtained from 6.46 g (0.03 mol) of N-BOC-4-hydroxymethylpiperidine (see EP 0 317 997), 4.9 g (0.03 mol) of N-hydroxyphthalimide, 7.87 g (0.03 mol) of triphenylphosphine, 5.3 ml (0.0317 mol) of azodicarboxylic acid diethyl ester (93 %) and 120 ml of tetrahydrofuran.

Example 6: 2-Aminooxymethylpiperazine trihydrochloride

A mixture of 2 g (0.00433 mol) of 2-(1,4-di-BOC-2-piperazinylmethoxy)-1H-isoindole-1,3(2H)-dione and 20 ml of 6N hydrochloric acid is heated under reflux for 2.5 hours and worked up analogously to Example 1. Recrystallisation twice from methanol/water/ether yields the title compound having a water content of 5.82 %, m.p. 130-135°C (decomp.).

The starting materials are prepared as follows:

a) 2-(1,4-Di-BOC-2-piperazinylmethoxy)-1H-isoindole-1,3(2H)-dione

Analogously to Example 4b, the title compound, m.p. 154-155°C, is obtained from 15.82 g (0.05 mol) of 1,4-di-BOC-2-hydroxymethylpiperazine, 8.16 g (0.05 mol) of N-hydroxyphthalimide, 13.11 g (0.05 mol) of triphenylphosphine, 8.85 ml (0.0529 mol) of 1,2-azodicarboxylic acid diethyl ester (93 %) and 100 ml of tetrahydrofuran.

b) 1,4-Di-BOC-2-hydroxymethylpiperazine

A solution of 34.4 g (0.1576 mol) of di-tert-butyl dicarbonate in 100 ml of acetonitrile is added dropwise at 5-10°C, with stirring, to a mixture of 8.71 g (0.075 mol) of 2-hydroxymethylpiperazine [see J. Med. Chem. 33, 142-146 (1990)], 100 ml of acetonitrile and 50 ml of water. The reaction mixture is stirred for a further 15 hours at room temperature and is then concentrated by evaporation *in vacuo*. Crystallisation of the residue from ethyl acetate/hexane yields the title compound, m.p. 120-121°C.

Example 7: 2-Aminooxymethylmorpholine dihydrochloride

10 ml of 2.2N ethanolic hydrochloric acid are added to a solution of 0.9 g (2.7 mmol) of N,N'-di-BOC-2-aminooxymethylmorpholine in 10 ml of ethanol, and the mixture is stirred at room temperature for 16 hours. The title compound which crystallises out is filtered off with suction, washed with a small amount of ethanol and ether, and dried, m.p. 185°C (with decomp.).

The starting materials are prepared as follows:

a) N-2-Hydroxyethyl-3-(1-ethoxyethylideneaminooxy)-2-hydroxypropylamine

8 ml (131 mmol) of ethanolamine are added to a solution of 6.4 g (49.6 mmol) of O-2,3-epoxypropylacetohydroxamic acid ethyl ester in 80 ml of isopropanol, and the mixture is stirred at 60°C for 16 hours. The reaction mixture is concentrated by evaporation and the residue is purified by chromatography on 250 g of silica gel with a mixture of methylene chloride:methanol 10:1 and then with methylene chloride:methanol:conc. ammonia 300:50:1. In this manner, starting material a is obtained in the form of a yellow oil,  $R_f$  value = 0.12 (silica gel/methylene chloride:methanol:conc. ammonia 300:50:1).

b) N,N'-BOC-N-2-hydroxyethyl-3-aminooxy-2-hydroxypropylamine

A solution of 5.2 g (23.6 mmol) of starting material a in 100 ml of 2N hydrochloric acid is boiled under reflux for 4 hours. After cooling, there are added in succession, with stirring, 100 ml of 2N sodium hydroxide solution, 200 ml of tetrahydrofuran, 2 g of sodium carbonate and a solution of 11 g of di-tert-butyl dicarbonate in 100 ml of tetrahydrofuran, and the mixture is left to react for 24 hours at room temperature. The two-phase reaction mixture is then diluted with 500 ml of ether. The organic phase is separated off, washed with water, dried over magnesium sulfate, filtered and concentrated by evaporation. The oil that remains is chromatographed over 250 g of silica gel with a mixture of hexane:ethyl acetate 1:1, yielding starting material b in the form of a yellow oil,  $R_f$  value = 0.06 (silica gel/hexane:ethyl acetate 1:2).

c) N,N'-Di-BOC-2-aminooxymethylmorpholine

A solution of 0.67 g (3.5 mmol) of tosyl chloride in 10 ml of methylene chloride is added dropwise at 0°C, with stirring and with the exclusion of moisture, to a solution of 1.2 g (3.4 mmol) of starting material b in 10 ml of pyridine. The mixture is stirred for one hour in an ice-bath and for 16 hours at room temperature, and then 1 ml of water is added and the reaction mixture is concentrated to dryness by evaporation. The residue is partitioned between 100 ml of ether and 50 ml of water. The organic phase is separated off, washed with water, with a saturated sodium hydrogen carbonate solution and again with water, dried over magnesium sulfate, filtered and concentrated by evaporation. The residue is chromatographed over 400 g of silica gel with a mixture of hexane:ethyl acetate 2:1, yielding starting material c in the form of white crystals,  $R_f$  value = 0.16 (silica gel/hexane:ethyl acetate 2:1), m.p. 106-108°C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.46 (s, 18H); 2.62-2.81 (t, 1H); 2.82-3.05 (t, 1H); 3.46-3.61 (m, 1H); 3.64-3.77 (m, 1H); 3.80-4.00 (m, 5H); 7.3 (s, 1H).

d) N,N'-Di-BOC-2-aminooxymethylmorpholine can also be prepared as follows:

2.2 g (14 mmol) of N-2-hydroxyethyl-3-aminoxy-2-hydroxypropylamine dihydrochloride are dissolved in 25 ml of dry hydrogen fluoride in a Teflon reactor at -78°C. 5.4 g (50 mmol) of sulfur tetrafluoride are introduced into that solution, the reactor is closed, and stirring is carried out at 0°C for 24 hours. The reactor is then degassed and the residue is dissolved in 20 ml of 2N HCl. The solution is filtered and, in succession, diluted with 100 ml of tetrahydrofuran and neutralised with solid sodium hydrogen carbonate, and a solution of 7.6 g of di-tert-butyl dicarbonate in 100 ml of tetrahydrofuran is added dropwise. The reaction mixture is stirred at room temperature for 16 hours and diluted with 100 ml of ether. The organic phase is separated off, washed with water, with a

saturated sodium hydrogen carbonate solution and again with water, dried over magnesium sulfate, filtered and concentrated by evaporation. The residue is chromatographed over 400 g of silica gel with a mixture of hexane:ethyl acetate 2:1, yielding starting material c in the form of white crystals,  $R_f$  value = 0.16 (silica gel/-hexane:ethyl acetate 2:1), m.p. 106-108°C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.46 (s, 18H); 2.62-2.81 (t, 1H); 2.82-3.05 (t, 1H); 3.46-3.61 (m, 1H); 3.64-3.77 (m, 1H); 3.80-4.00 (m, 5H); 7.3 (s, 1H).

Example 8: 2-Aminooxymethylmorpholine dihydrochloride

3.2 g (14 mmol) of N-2-hydroxyethyl-3-aminooxy-2-hydroxypropylamine dihydrochloride are dissolved in 25 ml of dry hydrogen fluoride in a Teflon reactor at -78°C. 5.4 g (50 mmol) of sulfur tetrafluoride are introduced into that solution, the reactor is closed, and stirring is carried out at 0°C for 24 hours. The reactor is then degassed and the residue is dissolved in 20 ml of 2N hydrochloric acid. The solution is filtered and concentrated to dryness by evaporation. The oily residue is taken up in a small amount of water and chromatographed over 200 ml of Dowex 1 ( $\text{Cl}^-$  form). The fractions containing the title compound are combined and concentrated by evaporation. The residue is crystallised from ethanol and ether, m.p. 185°C.

Example 9: 2-Aminooxymethylmorpholine dihydrochloride

A solution of 2.5 g (20 mmol) of the sodium salt of acetohydroxamic acid ethyl ester and 10.8 g (21 mmol) of 4-triphenylmethyl-2-(p-toluenesulfonyloxymethyl)morpholine [Chem. Pharm. Bull. 33, 3766 (1985)] in 50 ml of N,N-dimethylformamide is stirred at 100°C for 16 hours. After cooling, the reaction mixture is poured onto 400 ml of water. The resulting product is filtered off with suction, washed with water and taken up in 100 ml of ethanol. 100 ml of 2N hydrochloric acid are added to that solution, and the mixture is boiled under reflux for 4 hours, cooled and filtered, and the filtrate is concentrated by evaporation. The residue is crystallised from ethanol and ether, yielding the title compound, m.p. 185°C.

Example 10: 2-Aminooxymethylpiperazine trihydrochloride

10 ml of 2.2N ethanolic hydrochloric acid are added to a mixture of 0.45 g (1.35 mmol) of 2-(N-BOC-aminooxymethyl)-4-N-BOC-piperazine in 10 ml of ethanol, and the mixture is stirred at room temperature for 16 hours and then concentrated by evaporation in vacuo. Recrystallisation of the residue from methanol/water/ether yields the title compound, m.p. 130-135°C (decomp.).

The starting materials are prepared as follows:

a) N,N'-Di-BOC-N-2-tosyloxyethyl-3-aminoxy-2-tosyloxypropylamine

A solution of 1.34 g (7.0 mmol) of tosyl chloride in 10 ml of methylene chloride is added dropwise at 0°C, with stirring and with the exclusion of moisture, to a solution of 1.2 g (3.4 mmol) of N,N'-di-BOC-N-2-hydroxyethyl-3-aminoxy-2-hydroxypropylamine in 10 ml of pyridine. The mixture is stirred in an ice-bath for 16 hours, poured onto ice-water and extracted with ether. The ethereal phase is washed with water, with dilute ice-cold hydrochloric acid, with a saturated sodium hydrogen carbonate solution and again with water, dried over magnesium sulfate, filtered and concentrated by evaporation, yielding starting material a.

b) 2-(N-BOC-aminooxymethyl)-4-N-BOC-piperazine

A mixture of N,N'-di-BOC-N-2-tosyloxyethyl-3-aminoxy-2-tosyloxypropylamine in a 12 % ethanolic ammonia solution is heated at 100°C for 5 hours in an autoclave. The reaction mixture is then filtered and concentrated by evaporation, and the residue is taken up in ether. The ethereal solution is washed with dilute sodium hydroxide solution and with water, dried over sodium sulfate and concentrated by evaporation in vacuo, yielding starting material b (see Archiv der Pharmazie 291, 3 (1958)).

Example 11: 2-Aminooxymethylthiomorpholine dihydrochloride

Analogously to Example 10, 2-(N-BOC-aminooxymethyl)-4-N-BOC-thiomorpholine is treated with ethanolic hydrochloric acid, yielding the title compound.

The starting material is prepared as follows:

a) 2-(N-BOC-aminooxymethyl)-4-N-BOC-thiomorpholine

A mixture of N,N'-di-BOC-N-2-tosyloxyethyl-3-aminoxy-2-tosyloxypropylamine and sodium sulfide hydrate in ethanol is boiled under reflux for 4 hours. The reaction mixture is filtered and concentrated by evaporation, and the residue is taken up in ether. The ethereal solution is washed with water, dried over sodium sulfate and concentrated by evaporation in vacuo, yielding starting material a (see Austral. J. Chem. 9, 397 (1956)).

Example 12: 4-Aminooxypiperidine dihydrochloride

A mixture of 1.08 g (0.005 mol) of N-BOC-4-aminooxypiperidine and 25 ml of 1.3N

methanolic hydrochloric acid is stirred at room temperature for 8 hours and then concentrated by evaporation *in vacuo*. Recrystallisation of the residue from methanol/ether yields the title compound, m.p. 182°C (decomp.).

The starting material is prepared as follows:

a) N-BOC-4-aminooxypiperidine

A mixture of 3 g (0.00866 mol) of 2-(N-BOC-4-piperidyloxy)-1H-isoindole-1,3(2H)-dione (Example 1a)) and 17 ml of hydrazine hydrate is stirred at room temperature for one hour. 15 ml of water and 70 ml of ether are then added to the reaction mixture, and stirring is continued for a further 1.5 hours. Working up analogously to Example 5a) yields the title compound in the form of a crystalline residue, m.p. 51-52°C.

Example 13: 4-Aminooxypiperidine sulfate

20 ml (0.02 mol) of 2N sulfuric acid are added at room temperature, with stirring, to a solution of 2.32 g (0.02 mol) of 4-aminooxypiperidine in 50 ml of ethanol, and the reaction mixture is then cooled to 5°C. Filtering and washing the precipitate with ethanol and ether yield the title compound, m.p. 245-247°C (decomp.).

The starting material is prepared as follows:

a) 4-Aminooxypiperidine

A solution of 16 g (0.0846 mol) of 4-aminooxypiperidine dihydrochloride (Example 1, 2, 12) in 10 ml of water is introduced onto a column charged with Amberlite® IRA-400 (anion exchanger in the hydroxide form) and eluted with water. Concentration of the product-containing fractions by evaporation *in vacuo* at 40°C yields the title compound in the form of a colourless oil,  $R_f$ : 0.11 (silica gel thin-layer chromatography, eluant: methylene chloride/methanol/conc. ammonia 40/10/1 (v/v)).

Example 14: 4-Aminooxypiperidine benzenesulfonate

A solution of 3.16 g (0.02 mol) of benzenesulfonic acid in 30 ml of ethanol is added to a solution of 2.32 g (0.02 mol) of 4-aminooxypiperidine in 20 ml of ethanol. After concentration to a volume of approximately 25 ml, 30 ml of ether are added dropwise, with stirring. A crystalline precipitate forms and is filtered off and washed with ether. The title compound so obtained melts at 110-112°C.

Example 15: 4-Aminooxypiperidine adipate

50 ml of ether are added with stirring to a solution, at a temperature of 35°C, of 2.32 g (0.02 mol) of 4-aminooxypiperidine and 2.92 g (0.02 mol) of adipic acid in 70 ml of ethanol. Cooling to room temperature, filtration of the resulting crystalline precipitate and washing with ether yield the title compound, m.p. 97-98°C.

Example 16: Capsules each containing 0.25 g of active ingredient, for example one of the compounds according to Examples 1 to 15, can be prepared as follows:

Composition (for 5000 capsules)

active ingredient	1250 g
talc	180 g
wheat starch	120 g
magnesium stearate	80 g
lactose	20 g

The powdered substances are pressed through a sieve having a mesh size of 0.6 mm and mixed. 0.33 g portions of the mixture are introduced into gelatin capsules by means of a capsule-filling machine.